REMARKS

Claims 1-6, 8-13, 15-24, 26-31, 33-42, and 44-52 remain in the application. Claims 1, 19, and 51 have been amended. Claims 7, 14, 25, 32, and 43 have been cancelled. A version with markings to show changes made follows page 11. Reconsideration of this application, as amended, is respectfully requested.

Claims 1 and 19 have been amended to indicate that the biological sample comprises intact human tissue. Support for this amendment can be found at page 36, line 1 through page 40, line 6 of the specification. Claims 1 and 19 have been further amended to indicate that the biological sample is allowed to equilibrate at the first temperature before optical data are collected at the first temperature and the biological sample is allowed to equilibrate at the second temperature before optical data are collected at the second temperature. Support for this amendment can be found at page 34, lines 21-22 of the specification. Claims 1 and 19 have been further amended to specify that the physiological temperature range extends from 0 °C to 45 °C. Support for this amendment can be found at page 17, lines 4-6 of the specification and in claims 7 and 25, as originally filed.

Claim 37 has been amended to specify that the biological sample comprises intact human tissue. Support for this amendment can be found at page 36, line 1 through page 40, line 6 of the specification. Claim 37 has been further amended to specify that the physiological temperature range extends from 0 °C to 45 °C. Support for this amendment can be found at page 17, lines 4-6 of the specification and in claims 7 and 25, as originally filed.

Claim 51 has been amended to delete a redundant word. Claim 51 has been further amended to provide antecedent basis for the expression "disease state". Support for this amendment can be found at page 10, lines 10-15 of the specification.

Claim 51 was objected to for an informality, namely, the repeated word "is". This objection has been addressed by an amendment. Claim 51 was rejected under 35

applicant(s) regard as their invention. This rejection has been addressed by an amendment to claim 51.

Claims 1-3, 7-16, 19-21, 25-34, 37-39, 43-46, and 49 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13, 15, 33, and 35-36 of U. S. Application Serial No. 09/080,470 to Khalil et al. in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. Because this rejection is merely a provisional rejection and not an actual rejection, submission of a terminal disclaimer will be deferred in the subject applications until one of the applications has been allowed.

Claims 1-3, 6-21, 24-39, 42-51 were rejected under 35 U. S. C. § 103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. This rejection is respectfully traversed for the following reasons.

Mills, U. S. Patent No. 5,978,691 (hereinafter "Mills"), discloses a method for facilitating the noninvasive determination of characteristics of subject matter and the environment in which said subject matter exists, the method comprising the steps of:

Emitting at least one wavelength of electromagnetic radiation applied to said subject matter

Detecting said wavelength after contact with said subject matter

Inducing a temperature change in said subject matter while emitting and detecting said radiation applied to said subject matter

Computing parameters based on information processed from the contact of said radiation at various temperature levels on said subject matter.

Laufer et al., "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" (hereinafter "Laufer et al."), discloses the effect of

temperature on the optical properties of human dermis and subdermis as a function of near-infrared wavelength between 25 °C and 40 °C. Measurements were performed *ex vivo* on a total of nine skin samples taken from the abdomen of three individuals.

The claims of the present invention, as amended, recite the following features:

A. the temperature of the biological sample is set to a first temperature and the biological sample is allowed to equilibrate at the first temperature before optical data are collected at the first temperature, the first temperature being within the range of from about 0 °C to about 45 °C;

B. the first temperature of the biological sample is changed to at least a second temperature and the biological sample is allowed to equilibrate at the at least second temperature before optical data are collected at the at least second temperature, the at least second temperature being within the range of from about 0 °C to about 45 °C

C. the first temperature corresponds to a first depth of the biological sample;

D. the at least second temperature corresponds to a second depth of the biological sample.

Mills fails to disclose anything with respect to allowing a biological sample to equilibrate at a given temperature before optical data are collected at that temperature. Claim 19 of Mills recites that a temperature change is induced in the blood <u>while</u> radiation is emitted and detected through the blood. See column 17, lines 63-64 of Mills. Claim 34 of Mills recites that a temperature change is induced in the subject matter <u>while</u> radiation applied to the subject matter is emitted and detected. See column 19, lines 3-5 of Mills. These recitals indicate

that Mills teaches away from equilibration prior to the collection of optical data, because equilibration requires a significant delay prior to the collection of optical data.

In the present invention, light at at least one wavelength is introduced into a biological sample at a surface of the biological sample. Light that is reflected, scattered, absorbed, or emitted by the biological sample is measured from an **average sampling depth** that is confined within a temperature controlled region in the biological sample. A key feature of the present invention is the concept of average sampling depth. Average sampling depth can be characterized as the average light penetration depth in the biological sample over the range of wavelengths employed in the measurement. As shown in Table 1, page 31 of the specification, the average light penetration depth ranges from 0.72 mm to 2.04 mm over the wavelength range 550 nm to 900 nm. In Mills, the concept of average sampling depth is non-existent. In Mills, the light travels through the entire depth of the biological sample. Mills fails to disclose or suggest at what depth of the biological sample the blood vessels being observed are located. Each temperature used in the present invention corresponds to a particular depth in the biological sample. Even though Mills alludes to reflectance, Mills does not discuss the concept of **average sampling depth** in a biological sample.

Claims 1 and 19 have been amended to indicate that the tissue is an intact tissue. Laufer et al. can be used only with excised tissue. Thus, Laufer et al. teaches away from the use of a sample of intact tissue. Accordingly, the combination of Mills and Laufer et al. fails to render the claims of this application obvious for the following reasons:

(1) The method described in Laufer et al. is used only with excised tissue; the method of this invention is used with intact tissue;

(2) Mills performs optical measurements before the samples were allowed to equilibrate at the temperature at which optical data are collected; the method of this invention requires that the samples be allowed to equilibrate at a given temperature before optical data are collected;

method of this invention requires that the samples be allowed to equilibrate at a given temperature before optical data are collected;

(3) Mills is unaware of the effect of temperature change upon **average sampling depth** that is confined within a temperature controlled region in the body part; the method of this invention relies on the relationship between wavelength of the light used, temperature of the biological sample, and average sampling depth in the biological sample.

It should also be noted that the combination of Mills and Laufer et al. is a piecemeal reconstruction of the prior. A piecemeal reconstruction of the prior art cannot be a basis for a holding of obviousness. It is impermissible within the framework of 35 U. S. C. § 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to a full appreciation of what such reference fairly suggests to one of ordinary skill in the art. In the situation presented here, equilibration of the sample is chosen from Laufer et al., but the use of excised skin with measurements performed *ex vivo* (as shown in Laufer et al.) is excluded. The use of intact skin is chosen from Mills, but non-equilibration of the sample (as shown in Mills) is excluded. Moreover, Mills even teaches away from equilibration of the sample. Thus, the combination of Mills and Laufer et al. fails to render the claims of this application obvious to one of ordinary skill in the art.

Claims 4-5, 22-23, and 40-41 were rejected under 35 U. S. C. § 103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. and in view of U. S. Patent No. 5,782,755 to Chance et al. This rejection is respectfully traversed for the following reasons.

Chance et al., U. S. Patent No. 5,782,755 (hereinafter "Chance '755") discloses a scheme for monitoring one or more solutes in a biological system comprising the steps of : delivering light into a biological system containing one or more solutes, the light having a wavelength selected to be in a range wherein at least one of the one or more solutes is substantially non-absorbing; detecting at least first and second portions of the delivered light, the first portion having

biological system along one or more paths characterized by a second average path length that is greater than the first average path length; and comparing the first and second portions of the delivered light to monitor a concentration of one or more of the solutes in the biological system.

Claims 4 and 5 incorporate all of the features of claim 1; claims 22 and 23 incorporate all of the features of claim 19; claims 40 and 41 incorporate all of the features of claim 37. Each of these claims requires intact human tissue; each of these claims requires the biological sample to be equilibrated prior to performance of optical measurements; each of these claims requires the temperature at which the measurement is performed to correspond to a specific depth in the biological sample. Chance et al. '755 fails to remedy the deficiencies of the combination of Mills and Laufer et al. Accordingly, the combination of Chance et al. '755, Mills, and Laufer et al. fails to render claims 4-5, 22-23, and 40-41 obvious to one of ordinary skill in the art.

Claim 52 was rejected under 35 U. S. C. § 103 (a) as being unpatentable over U. S. Patent No. 5,978,691 to Mills in view of the journal publication "Effect of temperature on the optical properties of ex vivo human dermis and subdermis" by Laufer et al. and in view of U. S. Patent No. 5,873,821 to Chance et al. This rejection is respectfully traversed for the following reasons.

Chance et al., U. S. Patent No. 5,873,821 (hereinafter "Chance et al. '821"), discloses an oximeter disposed on an endoscope, catheter or guidewire or the like for insertion via a body passage to internal tissue, and including means such as an inflatable balloon to press the oximeter sensor against the localized tissue of interest.

Claims 4 and 5 incorporate all of the features of claim 1; claims 22 and 23 incorporate all of the features of claim 19; claims 40 and 41 incorporate all of the features of claim 37. Each of these claims requires intact human tissue; each of these claims requires the biological sample to be equilibrated prior to performance of optical measurements; each of these claims requires the temperature at which the measurement is performed to correspond to a specific depth in the biological sample. Chance et al. '821 fails to remedy the deficiencies

temperature at which the measurement is performed to correspond to a specific depth in the biological sample. Chance et al. '821 fails to remedy the deficiencies of the combination of Mills and Laufer et al. Accordingly, the combination of Chance et al. '821, Mills, and Laufer et al. fails to render claim 52 obvious to one of ordinary skill in the art.

In view of the foregoing, it is submitted that claims1-6, 8-13, 15-24, 26-31, 33-42, and 44-52, as amended, are in condition for allowance, and official Notice of Allowance is respectfully requested.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Once amended) A method of measuring at least one parameter of a biological sample, said method comprising the steps of:

(a) setting the temperature of said biological sample to a first temperature and allowing said biological sample to equilibrate at said first temperature before optical data are collected at said first temperature, said first temperature being within the [physiological temperature] range of [said biological sample] from about 0 °C to about 45 °C;

(b) performing an optical measurement on said biological sample at said first temperature;

(c) determining at least one optical parameter of said biological sample at said first temperature, said first temperature corresponding to a first depth in said biological sample;

(d) changing said first temperature of said biological sample to at least a second temperature and allowing said biological sample to equilibrate at at least said second temperature before optical data are collected at said at least said second temperature, said at least second temperature being within the [physiological temperature] range of [said biological sample] from about 0 °C to about 45 °C;

(e) performing said optical measurement on said biological sample at said at least second temperature;

(h) determining said at least one optical parameter of said biological sample at at least a second temperature, said at least second temperature corresponding to a second depth in said biological sample; and

(i) determining said at least one parameter of said biological sample from the functional relationship of said at least one optical parameter on depth in said biological sample , wherein said biological sample comprises intact human tissue.

19. (Once amended) A method of measuring at least one parameter of a biological sample having a plurality of layers, said method comprising the steps of:

(a) setting the temperature of said biological sample to a first temperature and allowing said biological sample to equilibrate at said first temperature before optical data are collected at said first temperature, said first temperature being within the [physiological temperature] range of [said biological sample] from about 0 °C to about 45 °C;

(b) performing an optical measurement on said biological sample at said first temperature;

(c) determining at least one optical parameter of a first layer of said biological sample, said first layer being located at a first depth of said biological sample, said first temperature corresponding to a first depth of said biological sample;

(d) changing said first temperature of said biological sample to at least a second temperature and allowing said biological sample to equilibrate at said at least second temperature before optical data are collected at said at least second temperature, said at least second temperature being within [said physiological temperature] the range of [said biological sample] from about 0 °C to about 45 °C;

(e) performing said optical measurement on said biological sample at said at least second temperature;

(f) determining said at least one optical parameter at at least a second layer of said biological sample, said at least second layer being located at at least a second depth of said biological sample, said at least second temperature corresponding to said second depth of said biological sample; and

(g) determining said at least one parameter of said biological sample from the functional dependence of said at least one optical parameter on depth in said biological sample , wherein said biological sample comprises intact human tissue.

37. (Once amended) An apparatus for measuring at least one optical parameter of a biological sample, said apparatus comprising:

(a) a means for irradiating a region of said biological sample with light;

(b) a means for collecting light re-emitted from said region of said biological sample;

(c) a means for changing the temperature of said biological sample to a temperature [within the physiological range of said biological sample] ranging from about 0 °C to about 45 °C so that radiation penetrates to a specified depth in said biological sample,

(d) a means for measuring the intensity of the collected re-emitted light at a plurality of temperatures, wherein the measured intensities correspond to light re-emitted from different depths of said biological sample; and

(e) a means for calculating at least one parameter of said biological sample from the dependence of at least one optical parameter on depth in said biological sample , wherein said biological sample comprises intact human tissue.

51. (Once amended) The apparatus of claim 37, wherein said at least one optical parameter is indicative of a disease state, wherein said disease state is [is] selected from the group consisting of diabetic state, vascular disease state, dermatological disease state, and neoplasmic disease state.